Sarcoidosis: A Case with Extensive Metastatic Calcification, Renal Failure and Favorable Response to Steroid Therapy

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SARCOIDOSIS being a disease that may involve almost any system of the body, a patient with this illness may have many different symptoms.[9,11] A high proportion of patients, on the other hand, may be asymptomatic and the diagnosis is often suggested only by routine x-ray films of the chest showing hilar lymphadenopathy. In 20 to 30 per cent of cases hypercalcemia and hypercalciuria occur,[15] which may cause a variety of symptoms, such as nausea and vomiting, and if uncorrected may lead to deposition of calcium in the kidneys, resulting in nephrocalcinosis and the signs and symptoms of renal insufficiency.[14,17] The hypercalcemia together with phosphorus retention, whether due to the renal insufficiency or secondary hypoparathyroidism, may lead to the deposition of calcium in other tissues, producing so-called ectopic or metastatic calcifications.

The following case is an example of such manifestations of the disease, again calling attention to the need to consider sarcoidosis in the differential diagnosis of hypercalcemia and chronic renal disease. It also demonstrates the remission which may be obtained with steroid therapy in the presence of extensive renal failure and metastatic calcifications. Since in this case the calcifications were unusually extensive, they are of particular interest.

CASE REPORT

The patient, a 27-year-old single white man, was admitted to the clinic service January 25, 1960 with chief complaint of headaches of ten years' duration.

A routine x-ray film of the chest in 1947 showed enlargement of the hilar shadows, suggesting hilar adenopathy. A right inguinal biopsy revealed only nonspecific fibrosis. X-ray films were taken periodically afterward but no enlargement of the hilar densities was noted.

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The patient was symptom-free until 1950, when he first complained of headache, gum pain and a "runny nose." X-ray films showed sinusitis, for which he was treated with drainage and antibiotics. Three years later he again complained of upper posterior gum pain, and "gritty" and "bloodshot" eyes. Antibiotics were administered for conjunctivitis and the condition abated. Pain also developed over the right temporomandibular joint and the right supraorbital area. Relief was obtained with aspirin, which was used frequently.

In November and December of 1953 the patient was admitted to hospital because of severe frontal headaches, nausea and vomiting. No abnormalities were noted in spinal fluid examination, an electroencephalogram and x-ray films of the skull. Anemia, two plus albuminuria, and elevation of the nonprotein nitrogen content to 111 mg. per 100 cc. were noted and an x-ray film of the chest showed a "central type of pneumonia involving the hilar area." An intravenous pyelogram showed no concentration of dye within the renal pelvices or calices, but films taken 90 minutes after injection showed some generally increased density of the renal shadows. The physician attending him at that time treated him symptomatically for chronic glomerulonephritis.

In March 1954 he was readmitted because of right low back pain radiating to the right inguinal area. He continued to complain of headaches. A retrograde pyelogram did not demonstrate any gross abnormality. Two blood transfusions were administered for persistent anemia. By November, 1954, headaches had become so severe that the patient required frequent injections of meperidine (Demerol®) for pain and was again admitted to the hospital. He also had recurrence of the vomiting, and large doses of analgesics and chlorpromazine (Thorazine®) were required to control these symptoms. Corticotropin, 20 units daily, was given for five days as additional treatment for his suspected chronic renal disease. The physician treating him believed that the symptoms were probably secondary to uremia. The blood urea nitrogen was 54 mg. per 100 cc. Cortisone, 75 mg. daily, was given for about three months without benefit.

In April 1959 the patient was again admitted because of progressive loss of hearing, was found to

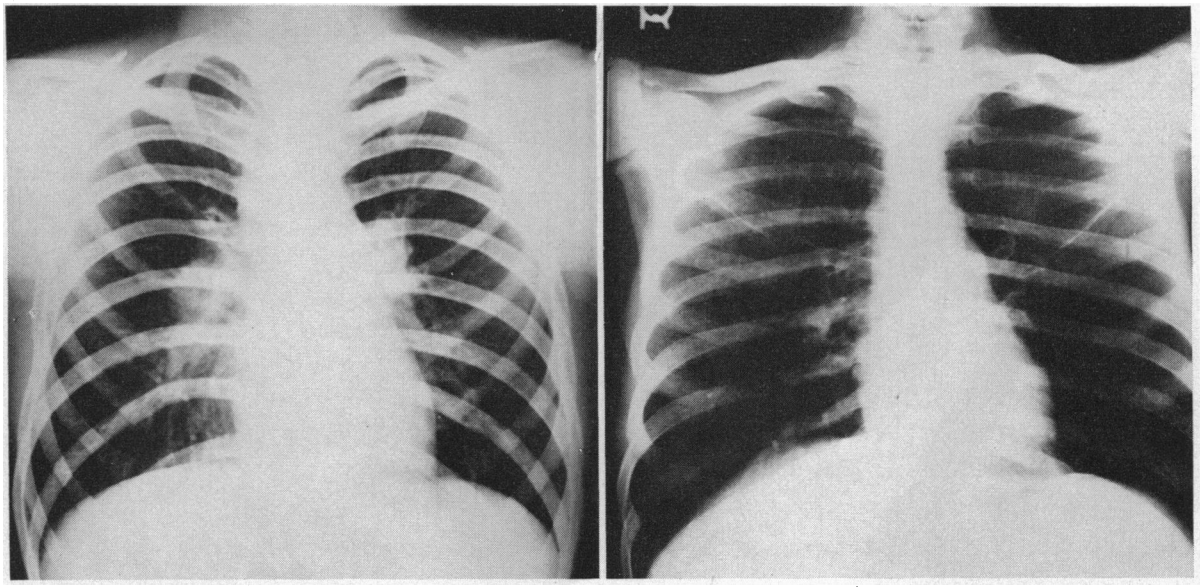

Figure 1.—X-ray film of the chest, showing hilar adenopathy in 1947 on the left and in 1960 on the right.

have fixation of the incus and stapes, and a stapes mobilization operation was performed. He was dealt with as an out-patient by his physician, and later in 1959 was noted to have diffuse calcification of the soft tissues about the ankle joints, the Achilles tendons and the calf muscles, enlargement of the spleen, and leukopenia. He was referred to our clinic and was admitted for further study. In addition to the severe headaches, he complained of difficulty in walking because of inability to bend his ankles. There was no history of excessive milk or alkali intake, or of large doses of vitamin D.

On physical examination the blood pressure was 120/90 mm. of mercury, the temperature 98.6° F. and the pulse rate 80. Hearing acuity was decidedly decreased on the right. The chest was clear to auscultation and percussion and the heart appeared normal. The spleen was palpable 9 cm. below the left costal margin. No adenopathy was present. The soft tissues extending from the midcalves bilaterally to the soles of the feet were firm, and the patient was unable to dorsiflex his feet because of fixation at the ankles. Four days following admission, diplopia developed. Complete paralysis in the area of distribution of the right sixth cranial nerve was noted. The ophthalmologist described extensive discrete, foamy deposits on the conjunctiva and on the gray line of the lower lids. No papilledema was present and the chambers were clear.

The hemoglobin content was 12.8 gm. per 100 cc. and leukocytes numbered 2,500 per cu. mm. of blood—54 per cent polymorphonuclear cells, 32 per cent lymphocytes and 8 per cent eosinophils. The urine reaction for albumin was 2 plus and for sugar negative. The specific gravity was 1.012. Serum calcium was 13.0 mg. per 100 cc. (normal 9 to 11.5) on one occasion and 12.7 mg. on another. Phosphorus content was 5.1 mg. per 100 cc. (normal 3 to 4.5 mg.) and when the determination was repeated was 6.2 mg. Alkaline phosphatase content was 2.3 units, albumin 3.75 gm., globulins 2.85 gm., urea nitrogen 58 mg. and uric acid 8.6 mg. per 100 cc. of blood. The spinal fluid showed normal pressure, protein content of 39 mg. and calcium 4.5 mg. per 100 cc. Bone marrow examination was reported as showing erythrocytic hyperplasia and "maturation arrest" of the granulocytic series at the polymorphonuclear level. The 24-hour urine contained 520 mg. of calcium and 1.04 gm. of phosphorus (normal calcium 50 to 300 mg. and phosphorus 2.25 gm. for 24 hours). Phenolsulfonphthalein excretion was 25 per cent in one hour and creatinine content of the blood was 3.6 mg. per 100 cc.

X-ray examinations showed increased bronchovesicular markings in the peripheral portion of the right upper lung field (Figure 1) and calcification of the soft tissues, especially the Achilles tendons, anterior tibial area and the plantar fascia and ligaments of the foot (Figure 2). Films of the skull showed extensive calcification of the falx cerebri and the tentorium cerebelli as well as the dural lining of both optic foramina (Figure 3). There was no apparent decalcification of the bones; in fact they appeared denser than usual. The lamina dura was observed in the dental films. An intravenous pyelogram showed no concentration of the dye after 90 minutes, and no calcification was seen within the kidney parenchyma.

To further evaluate the kidneys, a renal biopsy was done, and the pathologist reported extensive focal calcification (nephrocalcinosis). Almost all the glomeruli were completely obliterated by laminated and hyalinized fibrous scar tissue (Figure 4). Upon review of the case, sarcoidosis was considered and a scalene node biopsy was obtained. The pathologist reported a noncaseous granuloma

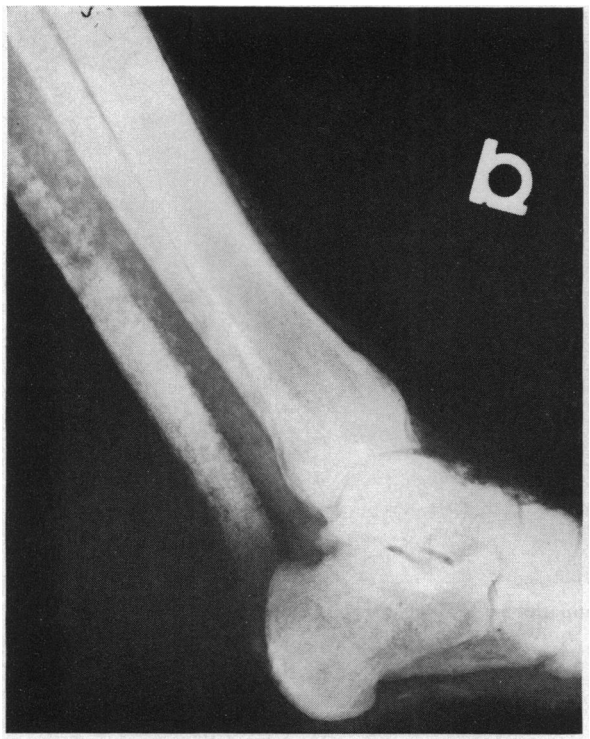

Figure 2.—X-ray film showing calcification in the soft tissues of the foot.

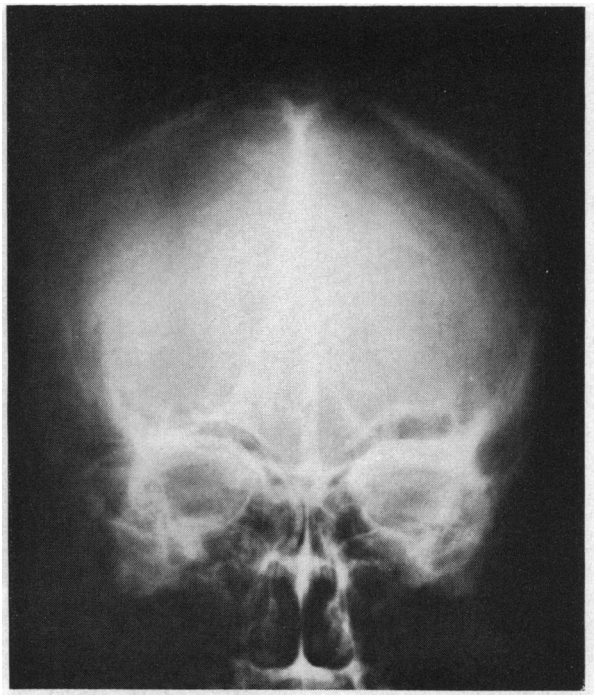

Figure 3.—X-ray film of the skull, showing extensive intracranial calcifications.

of the lymph node, consistent with sarcoid (Figure 5). Results of tuberculin tests were negative. A diet low in calcium and phosphorus was prescribed and the serum calcium decreased to 10.8 mg. and phosphorus to 4.8 mg. per 100 cc. in 12 days. The 24-hour urine calcium secretion was 213 mg. Administration of prednisone, 20 mg. daily, was then started. The headaches decreased in severity, and in five weeks were entirely gone. The spleen was no longer palpable. At the end of six weeks the patient was able to move the right eye laterally without difficulty. The serum calcium fell to 9.1 mg. and the phosphorus to 4.1 mg. per 100 cc. The 24-hour urine calcium was 152 mg. and blood urea nitrogen was 47 mg. per 100 cc. The dose of prednisone was reduced to 5 mg. daily.

In three months the serum calcium had reached a low of 8.9 mg. and the blood urea nitrogen 43 mg. per 100 cc.

The serum calcium had been maintained at between 9 and 10 mg. per 100 cc. for more than a year; then shortly before this report it began to rise. No Prednisone had been given for 11 days at the time of the rise in serum calcium. Therefore administration of it was resumed, first 5 mg. daily, then 10 mg. when the calcium level reached 11.0 mg. per 100 cc.

At the time of this report the patient was free of symptoms except for some difficulty in walking. Hemoglobin was 13.1 gm. per 100 cc. of blood, leukocytes numbered 5,350 per cu. mm. and serum calcium was 9.1 mg. per 100 cc.

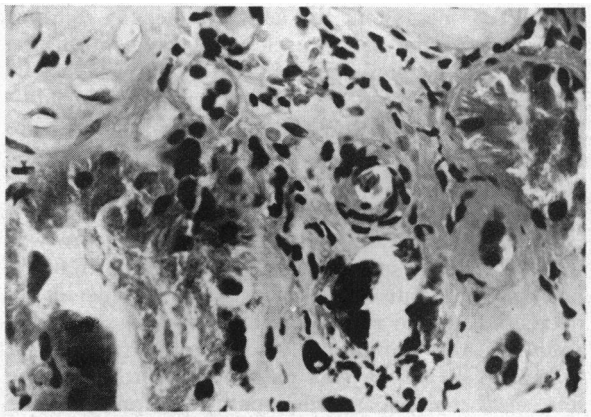

Figure 4.—Section of renal biopsy specimen (×100), showing nephrocalcinosis and hyalinized glomeruli.

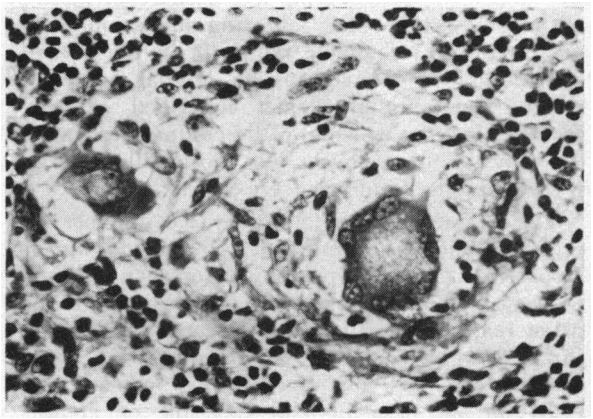

Figure 5.—Section of scalene lymph node (×100).

COMMENT

When this patient was first seen by us in 1960, he presented a perplexing problem of hypercalcemia, renal disease and extensive metastatic calcification. For many years he had been treated for what appeared to be chronic glomerulonephritis, and had been studied on several occasions for the possibility of cerebral lesion because of severe headaches, nausea and vomiting. The differential diagnosis of hypercalcemia may become very difficult, as it can occur in many diseases such as hyperparathyroidism, vitamin D intoxication, sarcoidosis, multiple myeloma and various malignant tumors, and the blood chemical features in these conditions may be confusingly similar.[19,20] The added complication of renal insufficiency with azotemia, as was seen in this patient, can further disturb the calcium and phosphorus levels, making the relationship of these ions of little value in differential diagnosis. The history of the patient, therefore, became important, and in view of the hilar densities seen in 1947, led to the suspicion of sarcoidosis. Although no lymphadenopathy was present on physical examination, the scalene node biopsy was fruitful in establishing the diagnosis. Renal biopsy revealed the true nature of the kidney disease by demonstrating the presence of the nephrocalcinosis which was not apparent by roentgenographic studies.

Nephrocalcinosis, renal calculi and corneal deposits are common ectopic calcifications in sarcoid. These may be the only presenting signs, and nausea and vomiting the only symptoms suggesting hypercalcemia. In mild hypercalcemia the calcium deposits in the eye may be the only clue to its presence.[4] This patient had unusually extensive calcification, involving structures within the skull and in the extremities. The calcifications of the lower extremities made it very difficult for the patient to walk because of the fixation of his feet at the ankle. By palpation it was hard to distinguish between these calcifications and the bones of the lower legs and feet. On x-ray the calcium deposits appeared almost as dense as the bones.

The headaches and sixth cranial nerve palsy in this patient were also outstanding symptoms. Sarcoid lesions of the nervous system are common in the cranial and peripheral nerves,[12] the seventh being the most frequently involved. Also posterior fossa and the hypothalamic-pituitary area are frequently involved.[18] The headaches and nerve palsy could be explained on the basis of granulomas in these areas, but the extensive calcifications around the brain may also have contributed to these symptoms. The deafness was also probably due to calcification immobilizing the bones of the inner ear. It has also been noted that hypercalcemia itself may be associated with neurological symptoms and elevation of the protein in the cerebrospinal fluid.[6] In the present case the protein and calcium contents of the spinal fluid were within normal limits.

Extensive calcifications have also been noted in vitamin D intoxication,[13,21] and the calcium disturbance in sarcoid is thought by some investigators to be secondary to a vitamin D sensitivity, resulting in increased absorption of calcium from the intestine.[8,10] The sequence of events leading to metastatic calcification (as ascribed to the first action of vitamin D by Albright and Reifenstein) may be increased calcium absorption, increased serum phosphorus levels, and a supersaturation of blood with respect to calcium phosphate, and its deposition in the tissues.[1,21] The renal insufficiency may also contribute to the elevated phosphorus. The early treatment of the patient with cortisone probably arrested the sarcoid, but not completely, so that a constant hypercalcemia persisted over the 13 years and the calcium deposits slowly built up to their present state. Although cortisone will reduce the hypercalcemia in sarcoid, some patients require maintenance therapy to keep the level within normal limits.[16] When steroids were stopped in this patient, serum calcium rose, then returned to lower levels after administration of prednisone was resumed. Improvement in renal function with steroid therapy has been reported even though renal calcinosis, as shown by serial biopsy,[5] remained unchanged. Correction of the hypercalcemia seems to be an important factor in the improvement,[5,7] provided extensive irreversible damage has not been done. Following steroid therapy, the patient in the present case had a reduction in serum calcium and blood urea nitrogen despite metastatic calcifications and severe renal damage from nephrocalcinosis. Absorption of peripheral ectopic calcifications with cortisone treatment has been reported,[2] and it will be of interest to observe this patient for resorption of the extensive calcium deposits.

SUMMARY

A case of sarcoidosis with renal insufficiency, nephrocalcinosis and extensive cerebral and peripheral calcifications is reported. The value of the history, renal and scalene node biopsy in addition to blood chemical determinations in making the diagnosis is emphasized.

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Vitamin D Intoxication

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HYPERCALCEMIA associated with renal insufficiency has been reported in numerous conditions such as vitamin D intoxication,[1,6] hyperparathyroidism,[3] acute osteoporosis,[2] sarcoidosis,[3,9,10] carcinomatosis with bone involvement,[3,12] multiple myeloma[3,11] and the "milk-alkali syndrome."[4] In 1942, two of the earliest cases in the literature of vitamin D poisoning in adults were described by Tumulty and Howard.[13] Since that time many reports have appeared and the clinical picture has been well described, particularly by Howard and Meyer[8] in 1948, and Chaplin and others in 1951.[7] Despite its toxicity, vitamin D still is sometimes used with little or no justification in conditions such as sarcoidosis, asthma, psoriasis and rheumatoid arthritis, and often results in poisoning. In addition, the general availability of highly concentrated preparations of vitamin D[7] has led to intoxication from self medication. Vitamin D intoxication has also been reported when the substance was being used for specific deficiency states such as osteomalacia secondary to steatorrhea and hypoparathyroidism after thyroidectomy.[5]

In the following case vitamin D intoxication occurred in a case in which a highly concentrated vitamin D product, Darthronol,®* was administered in the treatment of a musculoskeletal condition resembling early rheumatoid arthritis.

From the Santa Cruz Medical Center, Santa Cruz.
Submitted August 15, 1961.

*Darthronol; J. B. Roerig Co., Division Chas. Pfizer, Inc., N. Y.

REPORT OF A CASE

An insurance broker, age 33, otherwise in excellent health, consulted a physician November 6, 1958, because of pain in the forearms, wrists and hands. Darthronol® was prescribed, one tablet (50,000 units) the first day, two tablets the second, and then three daily. After a week of this therapy, the author examined the patient in consultation, and at that time he was complaining of general malaise, headaches, vertigo and pronounced polyuria and polydypsia. Upon physical examination in the office no abnormalities were noted. The urine had specific gravity of 1.009, an acid reaction and a negative reaction for albumin and sugar. On microscopic examination an occasional erythrocyte, 2 to 5 leukocytes and a moderate number of granular casts per high power field were noted. The Sulkowitch reaction was four plus. Vitamin D intoxication was suspected and the patient was advised to stop taking Darthronol®, to ingest no dairy products and to drink 2,500 to 3,000 cc. of plain liquids every 24 hours. He was again seen in his home two days later and the symptoms of headache and vertigo with nausea and vomiting persisted. Serum calcium at that time was 14.1 mg. and inorganic phosphorus content was 1.2 mg. per 100 cc. Because of the persistence of symptoms, the patient was admitted to the hospital for further observation and treatment.

On admission he was nauseated, but not in acute distress. The oral temperature was 98° F., the pulse rate 80 with regular sinus rhythm, respirations 20 per minute and blood pressure 140/90 mm. of mercury. Deep tendon reflexes were hypoactive to absent. The plantar response was flexor. Otherwise